UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte KEVIN H. GARDNER, CARLOS A. AMEZCUA,
PAULUS J.A. ERBEL, and PAUL B. CARD

Appeal 2007-2956
Application 10/677,733
Technology Center 1600

Decided: September 19, 2007

Before TONI R. SCHEINER, DEMETRA J. MILLS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 1 and 2. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

"PAS (Per-ARNT-Sim) domains are protein interaction domains widely used for intra- and intermolecular associations. . . . Some members of the PAS family are known to contain small molecules within their cores, allowing them to sense stimuli and regulate diverse biological processes.

For example, heme binding by the PAS domains of FixL . . . allows bacteria to sense oxygen levels" (Spec. 1). "However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998) show tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site" (Spec. 2). According to the Specification, "the invention provides methods of detecting binding of a PAS domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity" (Spec. 2).

Claims 1 and 2 are pending (App. Br. 1). Claim 1 is rejected under 35 U.S.C. § 103 as obvious over Fesik (WO 97/18471, May 27, 1997) in view of Edery (US 5,843,683, Dec. 1, 1998), Takahaski (US 6,291,429 B1, Sep. 18, 2001), or Berkenstam (US 6,436,654 B1, Aug. 20, 2002) (Answer 3). Claim 2 is objected to because it is dependent on rejected claim 1, but the Examiner states it would be allowed if rewritten in independent form (Answer 3). Claim 1 reads as follows:

> 1. A method of detecting binding of a PAS (Per-ARNT-Sim) domain with a foreign core ligand of the PAS domain, wherein the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity, the method comprising the steps of:
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> detecting a first NMR spectrum of the PAS domain in the presence of a foreign ligand; and
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> comparing the first NMR spectrum with a second NMR spectrum of the PAS domain in the absence of the ligand to infer the presence of the ligand specifically bound within the hydrophobic core of the PAS domain.

DISCUSSION

"[T]he Examiner bears the initial burden, on review of the prior art . . . , of presenting a prima facie case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed, Cir. 1992). *See* also *Hyatt v. Dudas*, 492 F.3d 1365, 1369-70, 83 USPQ2d 1373, 1375-76 (Fed. Cir. 2007).

The Examiner finds:

1) Each of Edery, Takahaski, and Berkenstam describe PAS domain proteins with hydrophobic cores, satisfying the limitation of claim 1 of a PAS domain which is "predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity" (Answer 4-6).

2) Edery, Takahaski, and Berkenstam teach identifying compounds which modulate the activity of the PAS domain protein (Answer 4-5).

3) Fesik teaches a method of identifying compounds which bind to proteins using NMR spectra (Answer 3).

The Examiner contends that it would have been obvious to have used Fesik's NMR method to identify compounds which modulate the PAS domain proteins of Edery, Takahaski, and Berkenstam because Fesik teaches that its method is "amendable to automation for identification of modulator of protein activity" (Answer 5).

The Examiner's case for prima facie obviousness is built on the presumption that the proteins described in each of Edery, Takahaski, and Berkenstam satisfy the claimed limitation of a PAS domain which is "predetermined, prefolded in its native state, and comprises a hydrophobic

core that has no NMR-apparent a priori formed ligand cavity." When the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing patentability is possessed by the prior art, "it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." *In re Swinehart*, 439 F.2d 210, 212-13, 169 USPQ 226, 228-29 (CCPA 1971). *See* also *In re Best*, 562 F.2d 1252, 1254-55, 195 USPQ 430, 433-34 (CCPA 1977); *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Thus, the issue in this appeal is whether there is a reasonable basis for believing that the prior PAS domain proteins meet the claimed limitation of "the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity."

In explaining the reason for the presumption that the prior art meets this claim limitation, the Examiner states:

> The linear amino acid sequence contains all the information required for proper folding of the protein to predetermined three-dimensional structure including any binding cavity required for its activity. Proteins are known to instantaneously fold during their biosynthesis. All folded proteins have hydrophobic core otherwise the protein would not fold.

(Answer 6.) Thus, the Examiner clearly states a reasonable basis for presuming that the PAS domain is in a "predetermined, prefolded in its native state, and comprises a hydrophobic core" as recited in claim 1. Appellants have not identified a defect in this reasoning, and we find none as it accurately reflects the knowledge of persons of ordinary skill in the art.

The claim further requires that the PAS domain "has no NMR-apparent a priori formed ligand cavity." We acknowledge that none of the

references cited for the teaching of PAS domain proteins describe the properties of the protein when imaged by NMR. With no explicit disclosure on whether the prior art PAS proteins possess an "NMR-apparent a priori formed ligand cavity," the first task is to determine whether there is any information that would lead persons of skill in the art to reasonably believe they do not as required by claim 1.

As pointed out by the Examiner, and not challenged by Appellants, the prior art PAS domains comprise a hydrophobic core. Persons of skill in the art would know that hydrophobic regions of a molecule would bond together, bringing the regions in close contact with each other.[1] In our opinion, this configuration would reasonably lead persons of skill in the art to infer that such regions do not have a ligand cavity in the native state, and that therefore, such cavity would not be detected by NMR, satisfying the limitation of claim 1.

In reaching this conclusion, we acknowledge that the Examiner erred in finding that "the PAS domains of the cited [prior] art must contain a binding cavity" (Answer 6; *see* Reply Br. 3, stating that the Examiner's assertion is "contrary" to the evidence of record). However, we do not find this misstatement fatal to the rejection. Nonetheless, because we have supplemented the rejection with reasoning of our own, we designate it as a new ground of rejection under 37 C.F.R. § 41.50(b).

In sum, we find that prima facie obviousness of the claimed subject matter has been established. First, the Examiner has provided a proper reason for combining the cited prior art. Secondly, a rationale has been

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[1] Darnell, *Molecular Cell Biology* 26 (2nd Edition, 1990).

provided to explain why it is reasonable for skilled persons in the art to believe that the prior art PAS domain proteins possesses the claimed limitation of "the PAS domain is predetermined, prefolded in its native state, and comprises a hydrophobic core that has no NMR-apparent a priori formed ligand cavity." Thus, there is sufficient evidence to shift the burden to Appellants to show that the claimed subject matter does not possesses the recited limitation.

Appellants contend that

> the prior work provided no evidence of cofactors for most PAS domains, and taught that those limited PAS domains having cofactors required them for proper folding, and taught that PAS domains without cofactors had tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site, one skilled in the art would not have suspected that such PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding; in fact, the art (supra) teaches squarely away from such use.

(App. Br. 5.)

We do not agree that "one skilled in the art would not have suspected that . . . PAS domains (without known cofactors and having tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site) would be rational candidates to screen for core ligand binding" (Appeal Br. 5). Takahaski suggests a method for identifying ligands for a PAS protein having a hydrophobic core (Answer 6). Edery also describes an assay method for identifying compounds that regulate a PAS domain protein's activity. Thus, despite the fact that these proteins have tightly packed cores with no pre-formed cavities – a fact that Appellants have not challenged – it was still suggested that these PAS domain proteins be

utilized for ligand screening (see, e.g., Takahaski, at col. 9, ll. 14-16; Edery, at col. 46-50).

Appellants state that a Declaration has been provided "documenting the fact that one skilled in the art would have considered the claimed invention nonobvious at the time it was made" (App. Br. 5). Paragraph No. 4 of the declaration (Declaration under § 1.132 by Dr. Stephen Sprang) repeats the same argument set forth in the Appeal Brief that we have already found to be unpersuasive.

Dr. Sprang states that he is "familiar" with the instant patent application, but he does not indicate his familiarity with the rejection at issue in this appeal nor the references cited in it. Moreover, he makes no mention of the references cited in the § 103 rejection, nor has he explained why the claimed invention is nonobvious over them. For this additional reason, we do not find the declaration sufficient to rebut the rejection.

The Specification refers to various prior art publications, including Morais Cabral (*Cell*, 95:649-655, 1998), for teaching "structurally characterized PAS domains without bound cofactors (. . . Morais Cabral et al., 1998) showing tightly packed cores with no pre-formed cavities that would suggest a cofactor or ligand binding site" (Spec. 2: 2-5). Morais Cabral, which Appellant admits satisfies the claim limitations for a PAS domain (App. Br. 5), compares the eag PAS domain of the HERG potassium channel to other PAS domain proteins known to comprise a ligand in their hydrophobic core (*see id.*, at 852, col. 2, describing the PYP photoreceptor which has a chromophore associated with its PAS domain). Morais Cabral conclude: "[g]iven the regulatory roles of PAS domains in other protein systems, we suspect that the eag domain will have a dynamic influence on

the gating of the HERG K^+ channels through the binding of small molecule or protein effectors" (*id.*, at 854, col. 2). Thus, despite having a tightly packed core with no pre-formed cavity, in view of its similarity to other PAS domain proteins, Morais Cabral suggested that small molecules might regulate eag domain activity as they do for other PAS domains.

In sum, we conclude that Appellants did not sustain their burden in rebutting the case of prima facie obviousness of claim 1. The rejection is affirmed.

TIME PERIOD

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) Reopen prosecution. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
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> (2) Request rehearing. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellants elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek

review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellants elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED; § 41.50(b)

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